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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/863,606 | 05/23/2001 | Julianna Lisziewicz | RGT 7028 | 2145 |

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The Law Offices of Valerie E. Looper
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| EXAMINER | |
|---|---|
| WILSON, MICHAEL C | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

DATE MAILED: 02/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/863,606 | LISZIEWICZ ET AL. | |
| | Examiner | Art Unit | |
| | Michael C. Wilson | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 November 2004 and 06 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *15,16,21-24,26 and 27* is/are pending in the application.

4a) Of the above claim(s) *15,16 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-24,26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's arguments filed 11-16-04 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-14, 17-20 and 25 are cancelled. Claims 15, 16, 21-24, 26 and 27 are pending.

### *Election/Restrictions*

This application contains claims 15, 16 and 21 drawn to an invention nonelected with traverse in the paper filed 5-12-03. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 15, 16 and 21 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 15, 16 and 21 have been mislabeled as "currently amended" in the amendment filed 12-6-04. In the future, the claims should be labeled as "withdrawn."

The original restriction/election was limited to administering the patentably distinct combination of ddI (an RT inhibitor) and indinavir (a protease inhibitor). The restriction is being maintained because i) RT inhibitors, protease inhibitors and hydroxyurea have different structures and functions, ii) the species of RT inhibitors in

claims 24 and 26 have different structures and inhibit RT using different mechanisms, iii) the species of protease inhibitors in claims 25 and 27 have different structures and inhibit protease using different mechanisms, and ii) the burden required to search administering all combinations of RT inhibitor species and protease inhibitor species together with administering DNA encoding an immunogenic retroviral protein would be undue.

Claims 22-24, 26 and 27 are only under consideration as they relate to administering antiretroviral drug therapy comprising ddI (an RT inhibitor) and indinavir (a protease inhibitor) until viral replication is suppressed, and then administering DNA encoding an immunogenic retroviral protein operably linked with a promoter.

Applicants' request for searches of other antiviral drugs has been denied.

***Specification***

The status of US Patent Applications on pg 4, line 28, pg 11, line 23, and pg 16, line 29, needs updated as necessary.

The amendment filed 3-11-04 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material that is not supported by the original disclosure is as follows: the specification does not support the changes made to the paragraph bridging pg 22-23 or the paragraph bridging pg 23-24. Applicant is required to cancel the new matter in the reply to this Office Action.

Applicants argue "Gilead Sciences (formerly, Gilead pharmaceuticals) uses the trade name Preveon® for a drug known variously as adefovir, adefovir dipioxil and PMEAV, the trade name Viread® for the drug know as tenofovir, tenofovir DF and PMPA; Glaxo Wellcome is now GlaxosmithKline; efavirenz (Sustiva®) was once owned by Dupont and is now owned by Bristol-Myers Squibb; lubocavir developed safety issues and is no longer available, and so has been deleted. Similarly, with respect to the paragraph bridging pages 23-24, Nelfinavir (Viracept®) has been available overseas from Roche, but is available from Auguoron in the US now. GW141, formerly available from Glaxo Wellcome/vertex, is no longer available and has been deleted. Tipranavir, formerly available from Pharmacia & Upjohn, is now available from Boehringer. An altemate generic drug name, atazanavir, and a trade name, Reyataz® have come into use for a Bristol-Myers Squibb material, BMS 232632." Applicants' argument is not persuasive. Unless the names were known at the time of filing, the trade names are new matter. Deleting drugs that are no longer available or that developed safety issues is new matter.

***Claim Objections***

The objections to the claims have been withdrawn in view of the amendment.

***Claim Rejections - 35 USC § 112 - enablement***

Claims 22-24, 26 and 27 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way

as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record.

Administering an antiretroviral drug therapy comprising ddI and Indinavir until retroviral replication is effectively suppressed is considered enabled because Finzi taught administering a reverse transcriptase inhibitor and a protease inhibitor suppressed retroviral replication (Finzi et al. Science. Nov. 14, 1997, Vol. 278, pg 1295-1300).

Claims 22-24, 26 and 27 require administering DNA encoding an immunogenic retroviral protein after administering the antiretroviral drug therapy. The sole disclosed purpose for administering DNA encoding an immunogenic retroviral protein is to induce an immune response against the retroviral protein that is therapeutic (pg 2, lines 14-19). Therefore, the step of administering DNA encoding an immunogenic retroviral protein must be fully enabled for using the DNA to obtain a therapeutic immune response against the "immunogenic retroviral protein". However, the specification does not enable using DNA encoding an immunogenic retroviral protein to induce a therapeutic immune response against a retrovirus in a host.

Claims 22-24, 26 and 27 are not enabled because the structure of the DNA encoding an immunogenic retroviral protein that provides a therapeutic immune response against the retroviral protein is not enabled.

The state of the art at the time of filing was that the combination of vector, promoter, route of administration, level of expression and target tissue required to obtain a therapeutic or prophylactic effect using gene therapy was unpredictable. Miller

of record (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain of record (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art that show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma of record (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal of record (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates, "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

The state of the art regarding treating retroviral infection was unpredictable. Stricker of record (Medical Hypotheses, June 1997, Vol. 48, pages 527-9) teaches that attempts to develop a vaccine against HIV have been unsuccessful because HIV vaccines do not neutralize HIV (pg 527, last paragraph through all of pg 528). Overall, a lack of understanding about protective immunity to HIV in humans, the sequence variability of HIV and the rapid replication of HIV contribute the ineffectiveness of vaccines against HIV (Bangham of record, Nov. 29, 1997, Lancet, Vol. 350, pages 1617-1621; page 1617, top of col. 1).

The specification teaches a complex comprising i) manosylated PEI and ii) DNA encoding an immunogenic HIV protein operably linked to a promoter. Administration of the complex to a host after drug therapy was followed by an increase in CD4 cells then a decrease in CD4 cells (pg 53).

The specification does not provide adequate guidance for one of skill to use DNA encoding an "immunogenic retroviral protein" to induce an immune response capable of treating a retroviral infection. The results described in the specification are not considered therapeutic because the overall result does not result in a net increase in CD4 cells. In addition, it cannot be concluded that the DNA encoding a retroviral protein caused the initial increase in CD4 cells because the experiment did not include controls - animals that did not receive drug therapy or the gene complex. The specification does not provide adequate guidance indicating the increase in CD4 was caused by an immune response to the retroviral protein encoded by the DNA - the drug therapy could have caused the increase in CD4. The specification did not teach treating animals that

were already infected or challenging the animals after they were given DermaVir. For administration of DNA encoding a retroviral protein to induce a therapeutic immune response, the specification must overcome the unpredictability in the art by adequately describing the structure of the "foreign genetic material" used, the dosage and route of administration that results in a therapeutic effect or "immunization." Without such guidance it would require one of skill in the art undue experimentation to overcome the unpredictability in the art regarding gene therapy and retroviral therapy to determine the combination of elements required to obtain a therapeutic or prophylactic effect against retroviral infection using "foreign genetic material. Therefore, the specification does not enable "therapeutic genetic immunization" using a gene delivery complex comprising "foreign genetic material" as claimed.

Applicants argue, "the present invention, and a therapeutic response is described in the application in Example 13" (pg 7 of response filed 11-16-04). Applicants argue the application shows more than CD4 results. Applicants argue the application shows reduced viral replication, i.e. "a reduction in the rate of viral rebound when drug treatment was stopped after vaccination (pg 53, lines 22-27; Fig. 14)" (pg 9 of response).

Applicants' arguments regarding Example 13 are not persuasive. Example 13 has been addressed in the rejection above. In summary, it cannot be concluded that the DNA encoding a retroviral protein used in Example 13 caused an increase in CD4 cells because the experiment did not include controls - animals that did not receive drug therapy or the gene complex. Example 13 does not provide adequate guidance

indicating the increase in CD4 was caused by an immune response to the retroviral protein encoded by the DNA - the drug therapy could have caused the increase in CD4. Example 13 did not teach treating animals that were already infected or challenging the animals after they were given DermaVir. Example 13 does not overcome the unpredictability in the art by adequately describing the structure of the "foreign genetic material" used or the dosage and route of administration that resulted in a therapeutic effect or "immunization" or that the DNA was responsible for any effect observed.

Applicants' arguments regarding pg 53, lines 22-27, and the reduced viral replication described in the specification are not persuasive.

The specification states:

> "The comparison of the rate of viral load rebound among those animals undergoing STI-HAART early after infection (Lori, F. et al. Control of SIV rebound through structured treatment interruptions during early infection. Science 290, 1591-1593. (2000)), those initiating STI-HAART during AIDS, and the same animals treated with STI-HAART plus DermaVir$_{SHIV}$ revealed an interesting pattern. The rate of viral rebound during consecutive HAART interruptions, that was unchanged before the initiation of vaccine therapy, decreased sharply after vaccination, and became remarkably similar to that observed in the animals treated with STI-HAART early after infection (Fig. 14). These results suggest that DermaVir$_{SHIV}$ therapy can improve the control of virus replication during interruption of HAAR." (pg 53, lines 18-27).

HAART therapy as described in Lori of record (2000) is PMPA (tenofovir, an RT inhibitor), ddI (didanosine, an RT inhibitor) and hydroxyurea (pg 1591, col. 3, lines 10-18). STI-HAART is structured treatment interruptions of HAART therapy.

The examiner agrees that the interrupted administration of PMPA, ddI and hydroxyurea followed by administration of DermaVir$_{SHIV}$ (AIDS(DermaVir)) in Fig. 14

shows decreased viral rebound as compared to interrupted administration of PMPA, ddI and hydroxyurea (AIDS(HAART)).

The claims are being considered as they relate to administering ddI and indinavir followed by a gene complex; however, the example is limited to administering PMPA, ddI and hydroxyurea followed by a gene complex. The combination of administering drugs plus DermaVir$_{SHIV}$ in the example does not correlate to administering ddI and indinavir plus DermaVir$_{SHIV}$. The specific combination of DermaVir$_{SHIV}$ with PMPA or hydroxyurea may have decreased viral rebound in the example. Perhaps the combination of two different RT inhibitors in the example with DermaVir$_{SHIV}$ decreased viral rebound (PMPA and ddI have different structures and different mechanisms of action (see DeClercq, Current Medicinal Chemistry, 2001, Vol. 8, pg 1543-1572; ¶ bridging pg 1553-1554; nucleotide vs. nucleoside analogues; "PMPA only needs two phosphorylation steps to be converted to the active metabolite"). The example does not use indinavir or any other protease inhibitor. The decreased viral rebound effect in the example may be a synergistic effect obtained only in the presence of PMPA, PMPA and ddI, or hydroxyurea. Therefore, one of skill would not expect DermaVir$_{SHIV}$ to decrease viral rebound after administering ddI and indinavir based on the example, which is limited to administering ddI, PMPA and hydroxyurea followed by DermaVir$_{SHIV}$.

Furthermore, the claims encompass administering continuous HAART followed by DermaVir$_{SHIV}$; however, the example is limited to interrupted HAART. The specification does not correlate decreasing viral rebound obtained by interrupting HAART followed by DermaVir$_{SHIV}$ with expected results obtained by administering

continuous HAART plus DermaVir$_{SHIV}$ (i.e. the virus does not rebound during continuous HAART). Therefore, mode of drug delivery in the example does not correlate to any mode of delivery as broadly encompassed by claim 21.

The claims encompass delivering any gene complex comprising DNA encoding any immunogenic retroviral protein; however, the example is limited to DermaVir$_{SHIV}$. The specification states:

> "DermaVir$_{SHIV}$ is a glucose-water solution containing a plasmid DNA as an active ingredient and polyethylenimine-mannose (PEIm) as an adjuvant (See Example 12). One therapeutic application contained 0.1 mg DNA capable of expressing all but the integrase protein of the Simian-Human Immunodeficiency Virus (SHIV). DermaVir$_{SHIV}$ was formulated to transduce Langerhans cells located in the epidermis and it was applied on the surface of the skin of the animals. We have shown that these Langerhans cells are triggered to migrate to the lymph nodes, mature to dendritic cells and present SHIV antigens to naïve T cells. After SHIV-specific activation of naïve T cells in the lymph nodes, DermaVir$_{SHIV}$ initiated potent SIV-specific T cell-mediated immune responses in uninfected monkeys (See Example 12)" (pg 52, lines 1-9).

The specification does not correlate the results obtained with DermaVir$_{SHIV}$, which expresses all retroviral proteins except integrase, to any DNA encoding any immunogenic retroviral protein as broadly claimed, specifically DNA encoding one immunogenic retroviral proteins, such as gp120. The expression of all retroviral proteins may be essential to induce the proper immune response and decrease viral rebound. (see pg 52, lines 1-9).

Not only is the gene complex itself much narrower in scope than the gene delivery complex claimed, the mode of delivery described in the specification is limited to dermal administration.

In conclusion, the example on pg 53 is much narrower than claim 21 in the types of drugs administered, the mode of delivery of the drugs, the gene complex being delivered and the mode of delivery of the gene complex. Decreasing viral rebound after interrupting two RT inhibitors and hydroxyurea cannot even be extrapolated to administration of ddI and indinavir because the combination of drugs in the example may have allowed DermaVir$_{SHIV}$ to function.

***Claim Rejections - 35 USC § 112 - indefiniteness***

Applicants' comments regarding claims 19-20 on pg 10 of the response filed 11-16-04 are moot because claims 19 and 20 have been canceled.

***The prior art***

Claims 22-24, 26 and 27 remain free of the prior art as they relate to administering antiretroviral drug therapy comprising ddI (an RT inhibitor) and indinavir (a protease inhibitor) until viral replication is suppressed, and then administering a DNA complex comprising a) DNA encoding an immunogenic retroviral protein operably linked with a promoter; and b) mannosylated polyethylenimine. The prior art did not teach or suggest administering ddI and Indinavir until viral replication is effectively suppressed, and then administering a gene delivery complex as claimed. Finzi (Science. Nov. 14, 1997, Vol. 278, pg 1295-1300) taught administering reverse transcriptase inhibitors and protease inhibitors to HIV patients. However, Finzi did not relate to administering DNA encoding the marker protein luciferase to the brain of mice as taught by Boussif (PNAS,

Aug. 1995, Vol. 92. pg 7292-7301) of record, administering DNA encoding a marker protein to cells *in vitro* as taught by Zanta (Bioconjugate Chem. 1997. Vol. 8. pg 839-844) of record, administering DNA encoding a marker protein to cells *in vitro* as taught by Behr (US Patent 6,013,240) of record, or administering virus encoding integrase-defective HIV to cells *in vitro* as taught by Cara (Virology, 1995, Vol. 208, pg 242-248).

The claims have not been searched for other antiviral drugs in combination with the gene complex as requested.

***Double Patenting***

Claims 22-24, 26 and 27 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,420,176 in view of the disclosure of 6,420,176 for reasons of record. The claims of '176 are directed toward a gene delivery complex comprising DNA encoding an immunogenic protein operably linked to a promoter and monosylated polyethylenimine. The claims of '176 do not require administration as required in the instant claims or administration of antiretroviral drug therapy. MPEP 804 states the specification may be used as a dictionary to learn the meaning of a term in the patent claim. In this case, one of skill would look to the specification to determine the asserted utility of the product. The disclosure taught administering the gene delivery complex after suppressing viral replication using antiretroviral drug therapy (col. 12, lines 11-51, see especially lines 20-27). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the gene delivery complex in combination with drug therapy as claimed.

Applicants argue the instant application shows unexpected results of the '176 patent by showing "the unexpected therapeutic efficacy of DermaVir SHIV in animals at a late stage of the disease reveals a previously unsuspected capacity of the host to response to the vaccination" (pg 53, lines 28-31). Applicants' argument is not persuasive. The statement on pg 53, lines 28-31, merely refers to interrupting administration of ddI, PMPA and hydroxyurea followed by dermal administration of $DermaVir_{SHIV}$ in mammals during late stages of AIDS. The statement cannot support an unexpected result for administering ddI+ indinavir followed by $DermaVir_{SHIV}$ or to the broad gene complex, mode of drug delivery, and mode of gene complex delivery encompassed by the claims.

Claims 22-24, 26 and 27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Application No. 10/081922 for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. Applicants argue '922 is a division of US Application 6,420,176 used in the obviousness-type double patenting rejection above. Applicants argue '922 is distinguished on the same basis. Applicants' argument is not persuasive and has been addressed above.

***Conclusion***

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

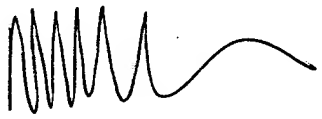
Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson



MICHAEL WILSON
PRIMARY EXAMINER